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Anatomy and physiology of the mineralized tissues: Role in the pathogenesis of osteoarthritis

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Summary

Synovial joints are composed of several different kinds of tissue that interact to protect normal joint function. Three subchondral mineralized tissues can be identified – calcified cartilage, subchondral cortical bone, and subchondral trabecular bone – which are distinguished morphologically, physiologically, and mechanically. Each responds to mechanical and pharmaceutical stimuli in different ways through processes of growth, modeling, and remodeling, and changes in each may have a distinct effect on the health of the joint. It is important to distinguish between the structural properties of these tissues and their material properties as these change differently in osteoarthritis (OA). It is likely that changes in the mineral content and thickness of the calcified cartilage play a greater role in the pathogenesis of OA than has been realized, whereas changes in trabecular bone are probably not causative. Changes in the subchondral cortical bone may accelerate progression of pre-existing disease, but the combined effects of increased subchondral bone turnover and greater subchondral bone volume are not at all clear. Ultimately, the efficacy of bone anti-resorptive therapies for OA will depend upon whether the increased structural stiffness of the subchondral mineralized tissues predisposes the cartilage to deteriorate, whether the increased bone turnover that occurs in OA is itself a causative factor, or whether the lower tissue elastic modulus offsets the increased structural stiffness of the subchondral plate in an attempt to protect the cartilage from damage.

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Introduction

Human joints are composed of several different tissues (cartilage, calcified cartilage, bone, synovium, ligament) that interact in unknown ways to allow joints to function relatively well over many years. These tissues are all important to the health of the joint, and when one tissue begins to deteriorate, it inevitably has an effect on the others. This ultimately leads to the failure of the entire organ (i.e., the joint). The most studied inter-relation in joint degeneration is between bone and cartilage. Bone is undoubtedly intimately involved in the initiation and progression of osteoarthritis (OA)^{1–5}. However, concentrating only on bone and cartilage provides an overly simplistic view of the joint in both health and disease, because in fact the joint is composed of other mineralized tissues that are differently organized, and which have different physiological and mechanical attributes.

This review concentrates on normal joint morphology and physiology, but relates these to the disease process that results in OA, and to potential therapeutic interventions. It emphasizes two concepts important to understanding how healthy joints function, and how mineralized tissues may be involved in the mechanical breakdown of a joint. First, subchondral mineralized tissues are not homogeneous; there are several different kinds of mineralized tissues in joints. These tissues respond to forces and drugs in different ways, not just through remodeling, but through processes of growth and modeling as well, even in

adults. The second concept is that the material properties of bone are different from the structural properties of bone. The strength and function of bone depend on both the properties of the tissue (the material properties) and on their geometric arrangement or architecture, a structural parameter. The bony sclerosis present in degenerating joints is a product both of density and architecture, and results from several distinct biological processes operating at different locations within the joint.

Normal joint anatomy

The primary bearing surface in a synovial joint is the articular cartilage (Fig. 1). The collagen and proteoglycans in the articular cartilage are arranged to withstand primarily tensile and shear stresses at the surface, and compressive stresses in the deeper cartilage layers⁶. Collagen tends to be oriented parallel to the surface in its superficial layers, and gradually is re-oriented to be perpendicular to the surface as one moves into the deeper radial zone just above the tidemark (i.e., the junction between the articular cartilage and the calcified cartilage)^{7,8}. At the same time, the proteoglycan content increases in the matrix from the articular surface to the tidemark⁶.

Deep to the articular cartilage, and separated from it by the tidemark, is a layer of calcified cartilage. The calcified cartilage is not very vascular normally, if it is vascular at all, and so the remodeling process is not going to be very effective here. But there is a process of ongoing endochondral ossification at the tidemark that can cause the calcified cartilage to thicken, and may contribute to subchondral sclerosis, as observed in radiographs (Fig. 2).

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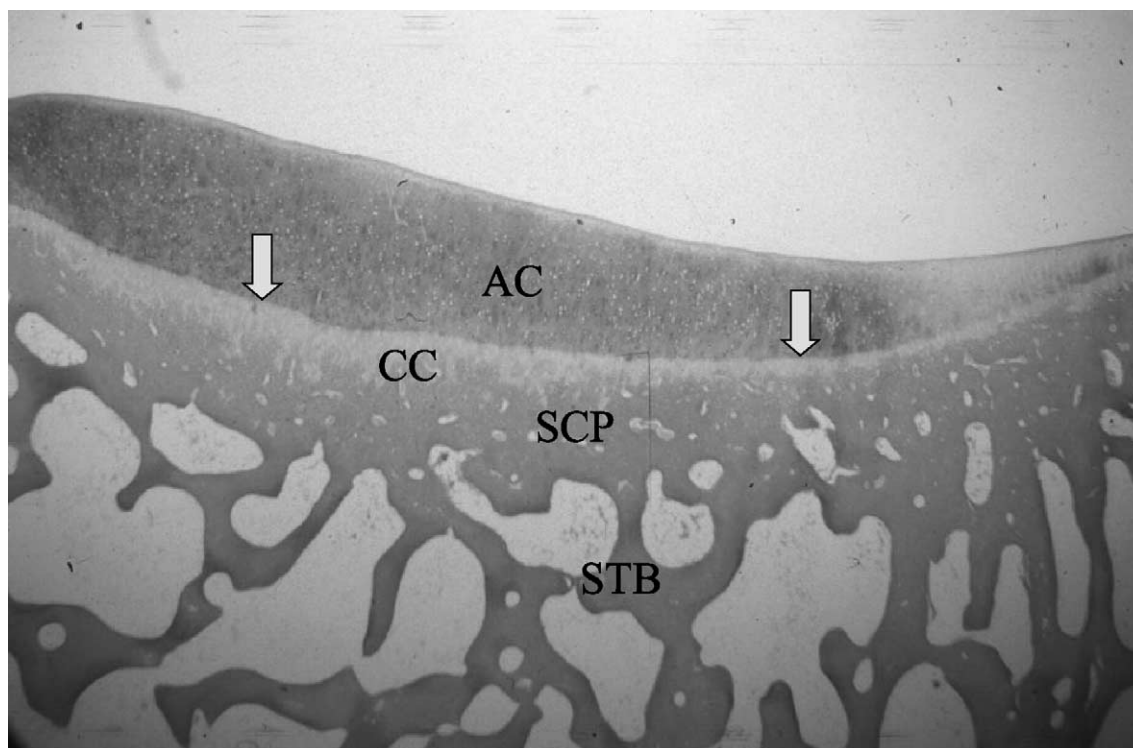


Fig. 1. Histological section showing the structure of a normal joint. The articular cartilage (AC) is separated from the calcified cartilage (CC) by an interface called the tidemark (arrows). The calcified cartilage forms an irregular boundary with the underlying subchondral bone plate (SCP). The SCP is architecturally distinct from subchondral trabecular bone (STB). Thus, there are at least three distinct mineralized tissues in the synovial joint, each one different morphologically, physiologically, and mechanically. (Safranin O, rabbit proximal tibia, Orig. mag.=6.25 \times)

Deep to the calcified cartilage is the subchondral bone plate, which is corticalized; it is not very porous and may not be very vascular. Subchondral bone may change its density by remodeling, but may also thicken through direct apposition of bone to its distal surface through a process called modeling.

Buttressing the subchondral plate from beneath is subchondral trabecular bone. Subchondral trabecular bone is clearly not homogeneous. It is anisotropic; that is, the trabeculae are oriented in different directions, and the mechanical properties of the tissue are therefore different in the different planes. Distinctions between the subchondral plate and subchondral trabecular bone are often not made clearly, but these two tissues are differently organized, adapt to mechanical loads in different ways, and have quite different mechanical properties^{9–11}. The three different mineralized tissues in the joint – calcified cartilage, subchondral plate, and subchondral trabecular bone – are different not only mechanically, but also physiologically. They respond to drugs and mechanical forces in different ways. An understanding of the interaction between subchondral mineralized tissues and cartilage in OA will depend on understanding these differences.

Growth, modeling, and remodeling in joints

In a normal, healthy joint, processes of growth, modeling, and remodeling occur constantly and throughout life, but are active to different degrees in the different mineralized tissues (Table I).

Growth is a process of tissue formation and increasing mass. There is no shape parameter associated with growth; it is simply the addition of material. Growth is often characterized by endochondral ossification at the growth plate. Since the growth plate is closed in adults, one might think that growth-related processes have ceased, but growth continues by a process akin to endochondral ossification at the tidemark^{12,13}. Consequently, the calcified cartilage continues to ossify at the tidemark (Fig. 3). Although this does not increase the length of the bone, it alters the mechanics of the joints and the nature and distribution of the forces that are applied to the overlying articular cartilage¹⁴.

Modeling is a process that primarily occurs in children. Modeling is defined as either formation or resorption at a given site, without the local coupling of these two processes. These processes increase bone mass, but also alter the shape of the bone. Although modeling generally occurs in children, it probably also occurs in specific locations in adults. Modeling processes – direct apposition of bone to the distal part of the subchondral plate – thicken the plate and may account for the stiffening of the subchondral plate that is associated with OA.

Modeling may also occur in trabecular bone, allowing trabecular struts to 'drift' through space to change trabecular architecture. But trabecular reorganization occurs primarily through remodeling, which employs a sequence of events at the same location (unlike modeling) to produce the change. Remodeling is characterized by the ARF sequence of events – activation, resorption and formation – at the same location (Fig. 4). In other words,



Fig. 2. Bony sclerosis is one hallmark of OA. (a) Radiographically normal hip joint; (b) hip joint from patient with advanced OA. Sclerosis in the diseased joint is marked by increased radio-opacity involving the femoral head and acetabulum (Reprinted with permission from Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage* 1995;3 Suppl A:3–70, with permission from Elsevier Science.)

Table I
The adaptation of mineralized tissues in a joint occurs by several different processes and mechanisms

Process	Mechanism*	Result
Growth	F (Formation)	Increased mass
Modeling	A-F (Activation-Formation) or A-R (Activation-Resorption)	Net increased mass; change in structural geometry
Remodeling	A-R-F (Activation-Resorption-Formation)	Bone maintenance
Repair	F (Formation)	Restore mechanical properties

* Activation, formation, and resorption occur in a sequence in different processes of growth, modeling, remodeling and repair.

resorption and formation are coupled in remodeling systems, and inhibiting resorption will suppress new bone formation as well. It is very difficult to uncouple resorption from formation.

During the activation phase of remodeling, processes at the cellular level are allowing for cell recruitment, differentiation, proliferation, and migration to surfaces (Fig. 5). This takes about 10 days in humans. This is followed by a resorption phase which lasts about 3 weeks. Resorption occurs for a certain duration and at a certain rate; cells can act more quickly, or they can act more slowly, and they can act for longer or shorter periods of time. Both duration and activity determine the amount of resorption that occurs. The reversal phase, the conversion between resorption and formation, takes about 5 days in humans. This is presumably when osteoblasts are recruited, although the processes involved in reversal are not well understood. Formation proceeds at this site for the next 3 months. The amount of formation at a given location is dependent, as is resorption, on cell activity and lifetime. It is important to stress that if any of the processes involved in ARF remodeling is changed – pharmaceutically or by any other means – all processes subsequent to it will also be

altered. In other words, reducing the activation frequency for remodeling will automatically reduce the amount of resorption and formation occurring in the tissue.

Following formation, the new bone is mineralized to a level of about 65% to 70%, fairly quickly. But 6 months to a year or more is required for the new bone to fully mineralize^{15–17}. The process of mineralization, which is necessary to achieve maximum density and stiffness of the bone, continues much longer than the process we call remodeling, measured histomorphometrically. There will be a lag time, normally on the order of weeks or months, and in disease conditions potentially of years, between the initiation of remodeling and the achievement of stiff bone.

Remodeling does not increase bone volume, but only maintains volume or causes bone loss. Because of this, remodeling processes cannot account for the sclerosis observed in OA. It is true that remodeling in the subchondral plate, and not just in the subchondral trabecular bone, is accelerated in advanced OA, but this would tend to decrease the density and stiffness of the bone, and not increase it.

These three processes affecting the calcified cartilage and bone are quite different. They affect different regions of

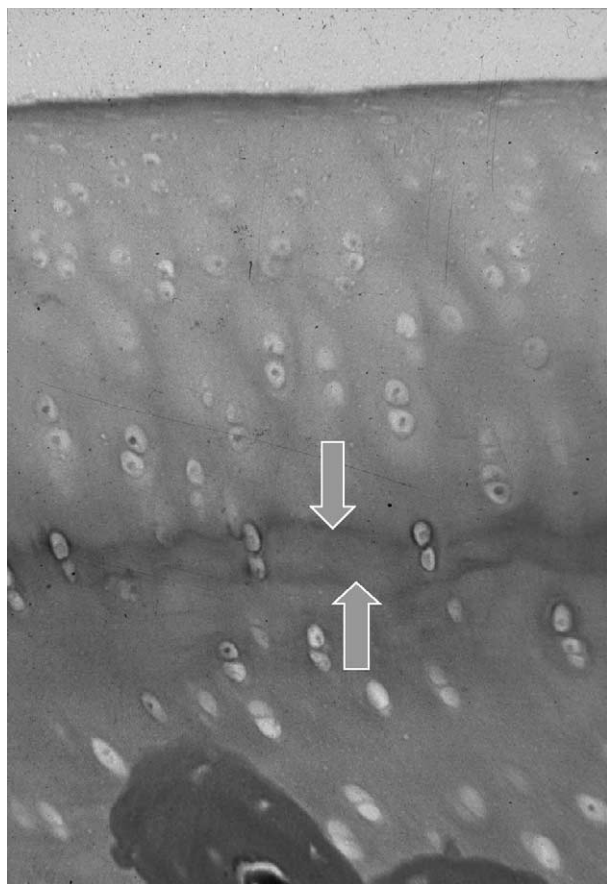


Fig. 3. Multiple tidemarks (arrows) are a common observation in animal models of OA, and also in aging human joints. Multiple tidemarks are an indication of continued endochondral ossification of the calcified cartilage. This section was taken from a sheep in which a cylindrical metal implant had been placed just beneath the subchondral cortical bone (Safranin O, Orig. mag.=62.5x)

a joint in very different ways, and they have different consequences for the mechanics of the joint. In turn, they are affected differently both by mechanical forces and by drug treatments.

Processes of skeletal adaptation in OA

CALCIFIED CARTILAGE

The process of endochondral ossification occurs throughout life. This causes advancement of the tidemark, which accounts for the duplication of the tidemark that is often observed in joints with degenerative disease (Fig. 3). Advancement of the tidemark is likely to make the calcified cartilage thicker, although whether it does so or not depends on the modeling processes that occur in subchondral bone. Even though the tidemark advances, remodeling at the osteochondral junction occurs more quickly, so that the calcified cartilage could become thinner. In a non-diseased joint, these processes of endochondral ossification and subchondral remodeling are generally in balance. In the diseased joint, they become out of balance. It is also possible that both tidemark advancement and subchondral remodeling accelerate in OA so that both the calcified cartilage layer and the subchondral bone thicken;

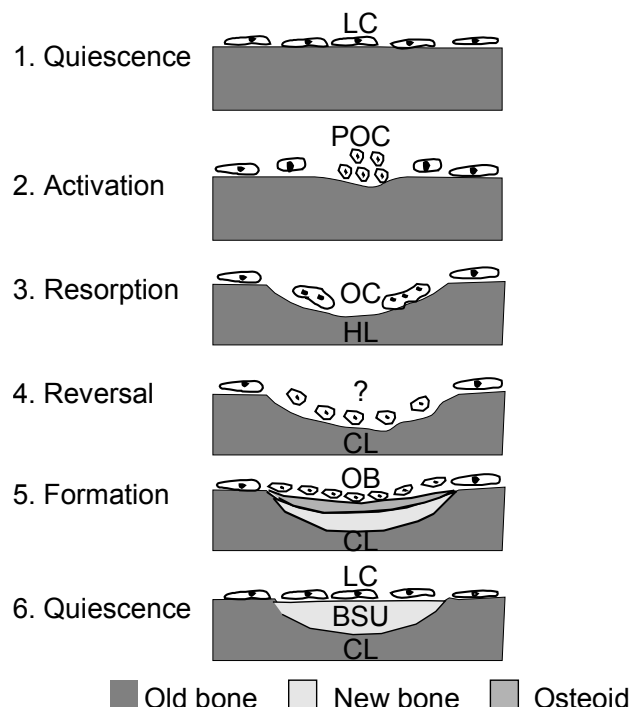


Fig. 4. Bone remodeling follows a well-defined series of events that begin with activation (A), followed sequentially by resorption (R), and formation (F). The process is sometimes called the A-R-F sequence of bone remodeling. The coupling between resorption and formation makes it particularly difficult to alter one of these processes without also altering the other. LC=lining cell; POC=preosteoclast (mononuclear); OC=osteoclast (multinucleated); HL=Howship's lacuna; CL=cement line; OB=osteoblast; BSU=bone structural unit. (Modified from Parfitt AM. Bone remodeling in the pathogenesis of osteoporosis. *Res Staff Phys* 1981;60-72. Used with permission of *Resident & Staff Physician*.)

this may underlie the subchondral sclerosis characteristic of OA.

This process has been demonstrated using the rabbit impulsive loading model developed by Radin and co-workers¹⁸. This is a model in which impulsive loads are applied to the hind limb of rabbits at 1.5x body weight, once per second for 40 min per day, 5 days/week, over periods of up to 9 weeks. Loads are applied by a cam-driven device, and the loaded limb is splinted to prevent a muscular contraction that would attenuate the load to the knee joint (Fig. 6).

It is established that loading rabbits in this way for 9 weeks will eventually lead, in 6 to 9 months, to full-thickness cartilage loss. The loading simply initiates a process of cartilage degeneration which continues to progress, even after the loading is stopped. After 9 weeks of loading, the thickness of the calcified cartilage is increased by about 25%, suggesting that the tidemark is advancing in these animals (Fig. 7). This is accompanied by a concomitant reduction in the thickness of the articular cartilage. Because the articular cartilage is thicker, the percentage reduction in thickness is smaller than in calcified cartilage, but the absolute reduction is not. The relationship between calcified and articular cartilage thickness in nondiseased joints is generally maintained and invariant within a species at a ratio of about 10:1^{19,20}. When this begins to change in early stage progressive OA, the stresses in the deep layers of the articular cartilage

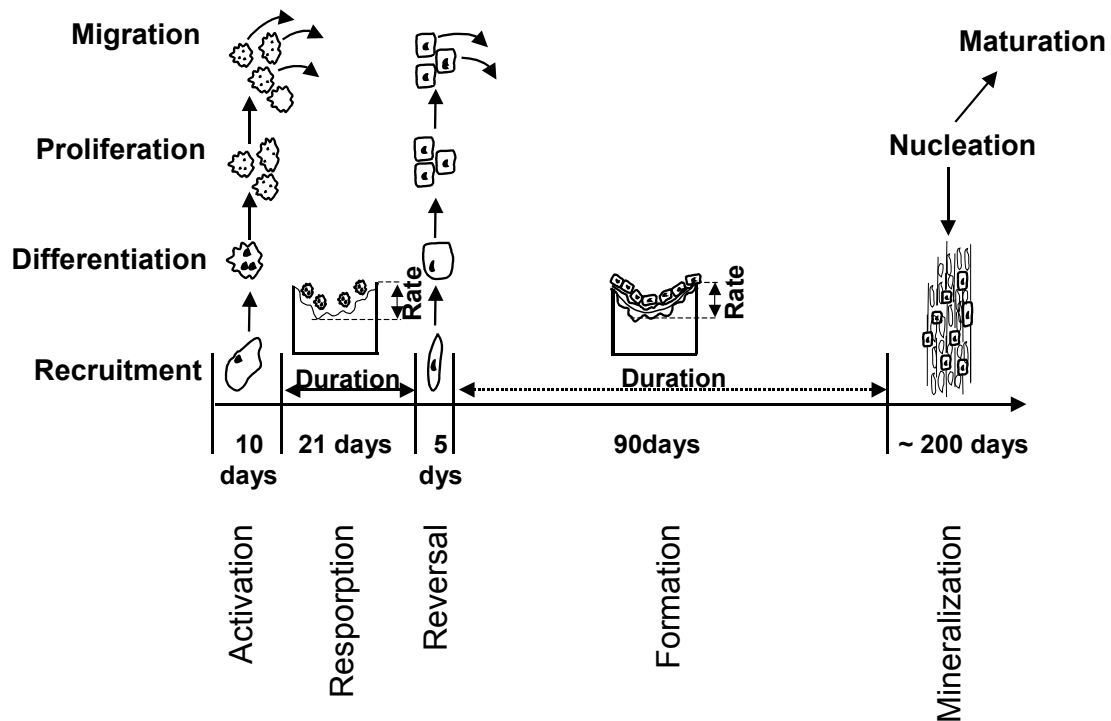


Fig. 5. Each of the processes in the A-R-F sequence involves many different activities at the cellular level, and take different periods of time. The entire sequence of events, not including mineralization, takes about 4 months in young, healthy humans. This is called the remodeling period (formerly called 'sigma'). Each process is governed by both a rate and a duration of activity. The times vary with age and with disease. (Reproduced from: Burr DB. Orthopedic principles of skeletal growth, modeling and remodeling. In: Bone Biodynamics in Orthodontic and Orthopedic Treatment. Carlson DS and Goldstein SA, Eds. Ann Arbor, MI: Center for Human Growth and Development, University of Michigan, 1992; pp. 15–50, with permission from the Center for Human Growth and Development.)

are likely to increase. Thus, in OA, there are structural changes to calcified cartilage that could be associated with radiographic sclerosis, and that could cause the cartilage deterioration to progress to complete loss.

There may also be changes to the material properties of the calcified cartilage. Conventional wisdom holds that calcified cartilage provides a layer of intermediate stiffness between the relatively compliant articular cartilage and the much stiffer subchondral bone¹¹. From a mechanical standpoint, this would reduce the stress concentrations that would inevitably occur at the junction of two tissues with very different stiffnesses. But in fact, this may not be true at all. Backscattered electron microscopic images show that the calcified cartilage is more mineralized and denser than subchondral bone (Fig. 8). This will increase the stiffness of the calcified cartilage, and could have significant effects on stresses in this tissue when it is loaded²¹.

The increased mineralization of the calcified cartilage can be quantified. We took portions of cartilage and subchondral bone from two regions of human femoral heads (both genders, ages 16–90, $N=19$) from the dissecting room. Two sites were sampled, one at the zenith of the femoral head in an area generally considered to be weight-bearing (Site A) and the other from a non-weightbearing site inferior to the fovea capitis. These two sites were chosen because one is under high compressive loads during locomotion, and the other is probably not. Mineral content in the calcified cartilage and subchondral bone at these two sites was quantified using electron microprobe analysis. At both sites, the calcified cartilage was significantly denser, and had significantly more mineral, than the adjacent subchondral bone (Figs. 8 and 9). Thus,

the calcified cartilage may not form a layer of intermediate density and stiffness between the articular cartilage and the subchondral bone. This could have significant implications to the long-term health of a joint. Although the relationship between bone and cartilage in OA has been widely discussed, the calcified cartilage also may play an important role in the initiation and/or progression of OA.

SUBCHONDRAL BONE AND SUBCHONDRAL TRABECULAR BONE ARE DIFFERENT

Subchondral bone (i.e., the corticalized subchondral plate) and subchondral trabecular bone are different, and are subject to different kinds of physiological processes. The term 'subchondral bone' is often used for both regions, without proper distinctions for their physiological and mechanical differences. And yet, the changes that occur in the subchondral plate are quite different from the changes that occur in the trabecular bone, at least in late stage disease.

In preparations of dry bone, subchondral plate and trabecular bone are similar in appearance. The subchondral plate appears to differ from the underlying trabecular bone only in being a little less porous. But the physiological processes that allow the joint to adapt are quite different in these two locations. And the significance of changes in density and stiffness in these two locations to the degenerative processes in the joint are also quite different. A finite element analysis of a stiff cylindrical metal implant placed in the subchondral bone of a sheep tibia suggests that stiffening trabecular bone more than about a millimeter and a half from the osteochondral junction will

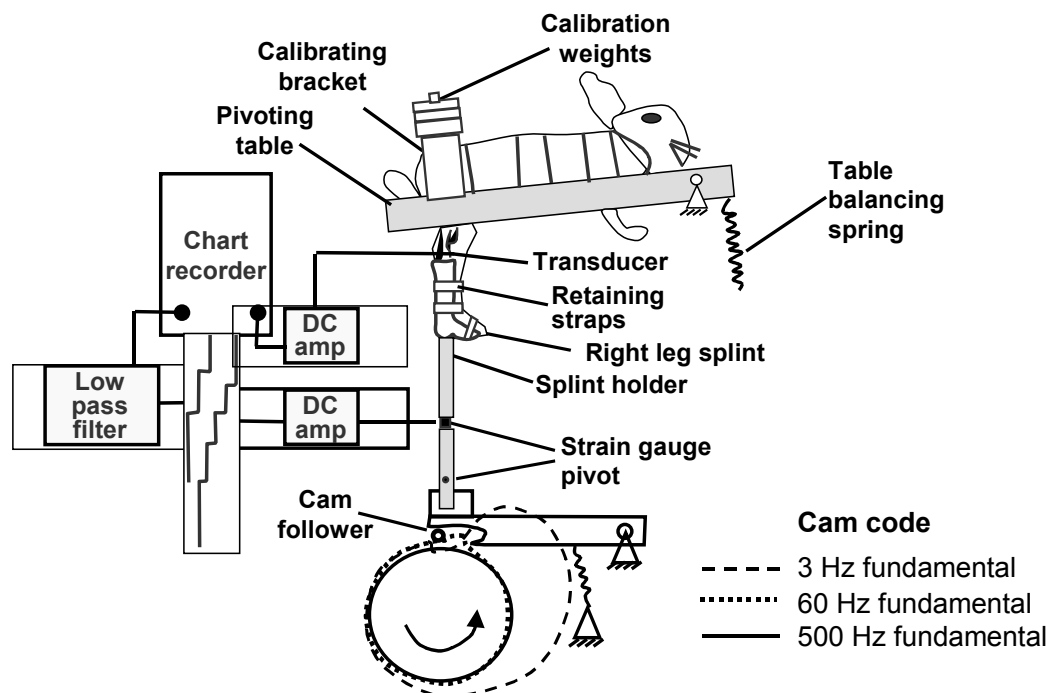


Fig. 6. The impulsive loading model of OA developed by Radin and co-workers uses a cam-driven device to apply loads to the rabbit hindlimb. The rabbit's leg is splinted to prevent contraction of the gastrocnemius muscle which could attenuate the load. Loads are typically applied at 1.5× body weight and 1 Hz for 40 min/day, 5 days/wk, over the course of 3 to 9 weeks. Even without additional loading, cartilage deterioration will progress to complete cartilage loss within 6 months. (Reprinted from Paul IL, Munro MB, Abernethy PJ, Simon SR, Radin EL, Rose RM. Musculoskeletal shock absorption: Relative contribution of bone and soft tissues at various frequencies. *J Biomech* 1978; 11:237–239, with permission from Elsevier Ltd.)

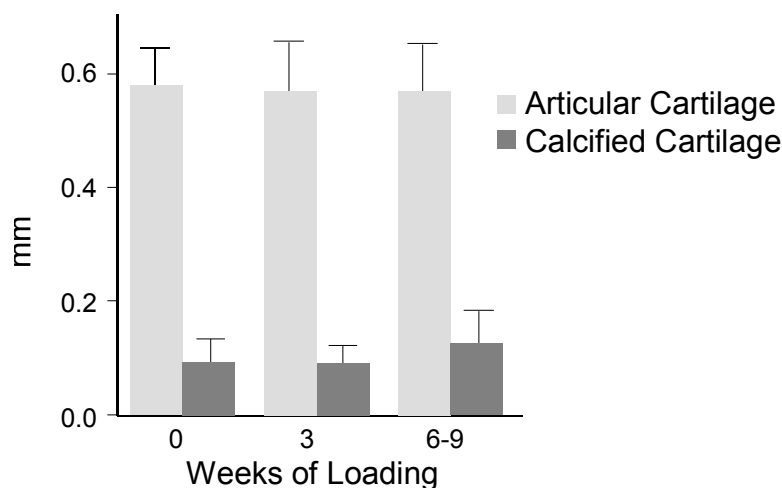


Fig. 7. Changes in thicknesses of the articular and calcified cartilage of the rabbit proximal tibia at baseline ($N=7$), and after 3 ($N=6$) or 6–9 ($N=9$) weeks of repetitive impulsive loading. After 6–9 weeks of loading, the thickness of the calcified cartilage has increased by about 25%, presumably as a function of tidemark progression ($P<0.09$). Because new articular cartilage does not form, its thickness declines commensurately as the tidemark advances. This would increase cartilage stresses upon loading. (Reproduced from Reference ³ with permission from John Wiley & Sons, Inc.).

have no effect on stresses in the cartilage, even in the deep layers of cartilage²¹. Increased densification of the subchondral plate (or calcified cartilage) within 1.5 mm of the tidemark will increase stresses in the deep layers of the cartilage by about 50%.

There is agreement in the findings of most studies that the trabecular bone volume in OA increases by about 20%²², and this, in part, accounts for the subchondral

trabecular sclerosis observed in the later phases of the disease. The increase in trabecular volume occurs mainly through an increase in trabecular number and reduced separation between trabeculae, rather than through thickening of the trabeculae.

At the time that one observes increased subchondral density, there is an increased rate of bone turnover so that the tissue present is newly formed, and may not be well

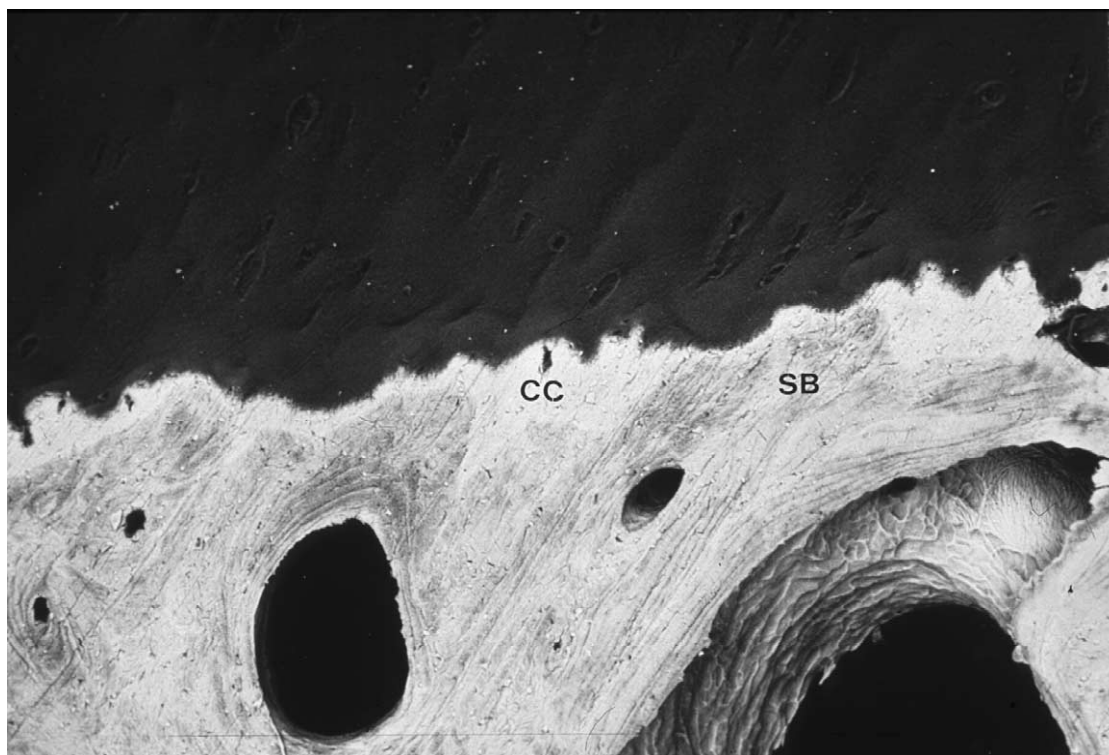
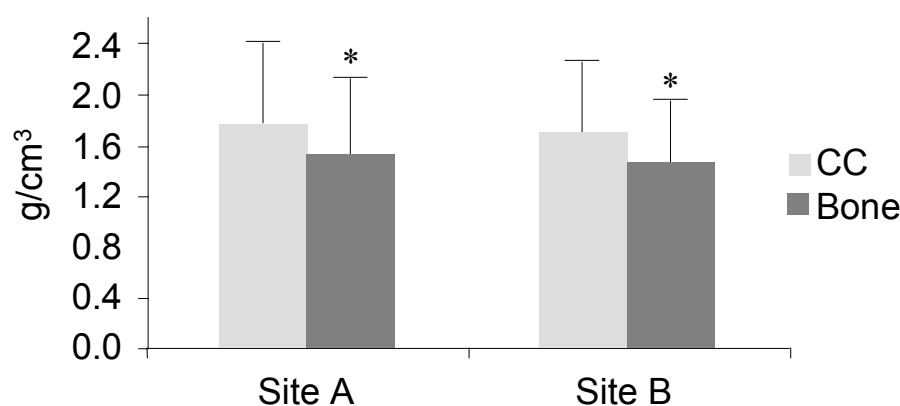


Fig. 8. Backscattered electron microscopic image of the cartilage and bone taken from a non-weightbearing site inferior to the fovea capitis of the femoral compartment of the hip joint. The calcified cartilage (CC) is clearly demarcated from the articular cartilage superior to it, and from subchondral bone (SB) beneath it. The calcified cartilage is more electron dense than the subchondral bone, suggesting the calcified cartilage is more highly mineralized. (Orig. mag.=100 \times .) (Reprinted from Burr DB. Subchondral bone in the pathogenesis of osteoarthritis. Mechanical aspects. In: Osteoarthritis. Brandt KD, Doherty M and Lohmander (eds.). Oxford University Press, 2003, p. 125.)



* $P < 0.001$, when compared to calcified cartilage mineral content (paired t-test)

Fig. 9. Mean mineral content of calcified cartilage (CC) and bone measured using contact microradiography from the superior surface of the femoral head (Site A) and from the inferior surface of the femoral head (Site B). Grey values were measured on five or more randomly chosen areas of one section from each of 19 individuals using an image analysis system. Values were converted to mineral content using standard formulae normalized to an aluminum step wedge. The total area measured for calcified cartilage in each section ranged between 10–41 mm² and for subchondral bone between 10–50 mm². Calcified cartilage was significantly ($P < 0.001$) more mineralized than subchondral bone at both sites.

mineralized. Density gradient profiles in subchondral bone and in trabecular bone from osteoarthritic individuals, age-matched older controls, and young controls show a shift from higher density bone, or from more mineralized bone, to lower density, more poorly mineralized bone (Fig. 10)²³.

The older controls and the younger controls, neither of which are arthritic, are not different from each other.

Thus, a distinction must be made between bone's apparent density, defined as bone mass/total volume, and bone's material density, defined as bone mass/bone

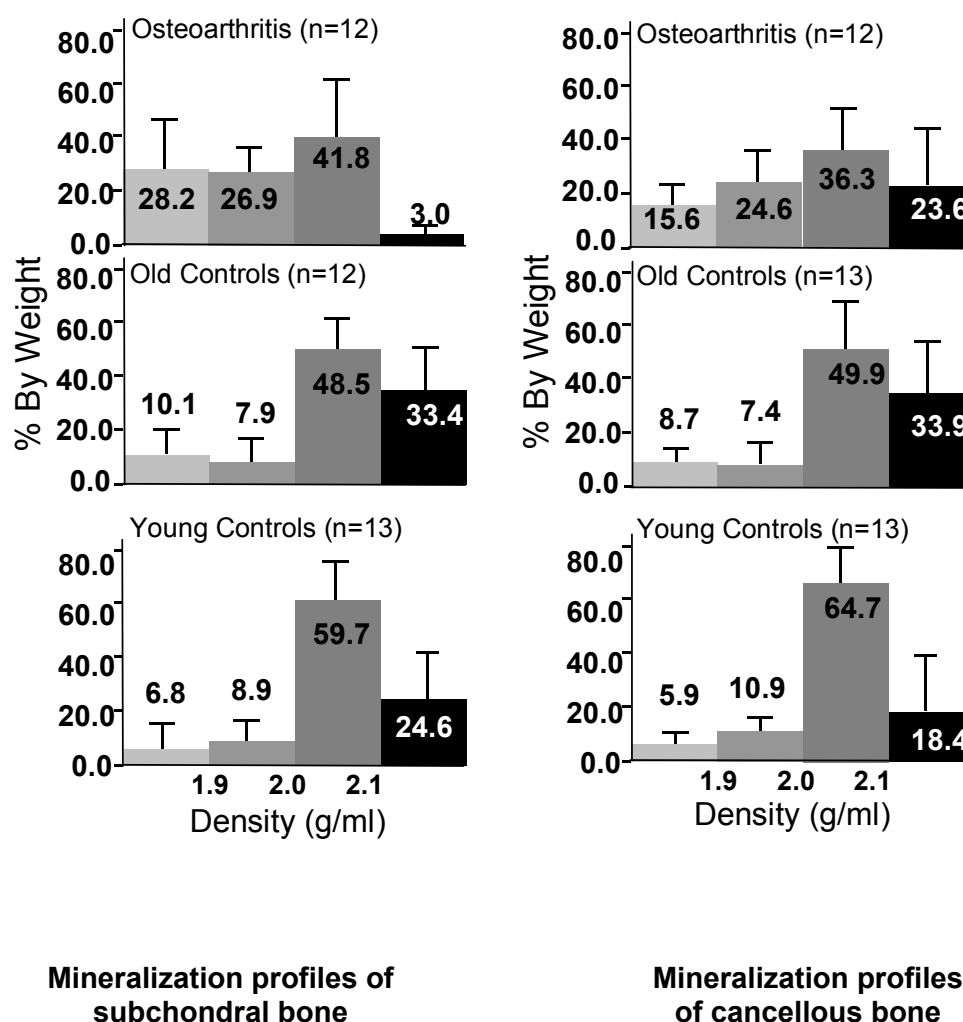


Fig. 10. In OA, joint degeneration is associated with a shift to lower density bone, compared either to young controls or to old, non-OA controls. This is probably a consequence of the increased rate of turnover. This suggests that, although there may be an increased bone volume in OA, the mineralization and elastic modulus (material stiffness) of the tissue itself are reduced. (Reprinted from Reference ²³ [Figs. 2 and 4] with permission from Springer-Verlag.)

volume. The apparent density is a structural property that increases in response to either an increase in mineralization of the tissue or an increase in bone volume. The material density can decrease with increased bone volume if the mineralization of a unit of tissue has decreased, for example in response to increased bone turnover.

Li and Aspden²⁴ showed that although the apparent density of bone in osteoarthritic patients is significantly greater than in normal or osteoporotic individuals, the material density is significantly less (Fig. 11). This is because, even though bone volume may increase, an increased rate of bone turnover will reduce the overall level of mineralization of the tissue, i.e., reduce the density of the bone material itself. The increased rate of bone turnover in deteriorating joints can be demonstrated in stained sections from arthritic joints (Fig. 12), but also can be detected biochemically by changes in alkaline phosphatase, osteocalcin, or other biochemical markers²⁵.

This demonstrates a fundamental mechanical concept that is important to understanding the health and deterioration of joints: the structural properties and the material properties of bone are different. What the joint "sees" and responds to is the overall structural stiffness of the

mineralized tissues beneath the cartilage. This structural property reflects the combination of the material properties and trabecular architecture, or the apparent density. It is the apparent density that one sees radiographically and which accounts for the observation of subchondral sclerosis.

Implications for treatment of OA

As outlined above, modeling and remodeling differ in several significant ways, and consequently one might expect that they will respond differently to therapeutic agents designed to alter the processes of resorption or formation. The sequence of events associated with modeling involves activation and resorption or activation and formation at a single site, but resorption and formation do not occur at the same locations. Remodeling, on the other hand, involves sequential processes of resorption and formation at the same site. Therefore, a drug treatment designed to suppress the elevated subchondral remodeling associated with joint degeneration by reducing resorption (e.g., bisphosphonate, non-steroidal anti-inflammatories

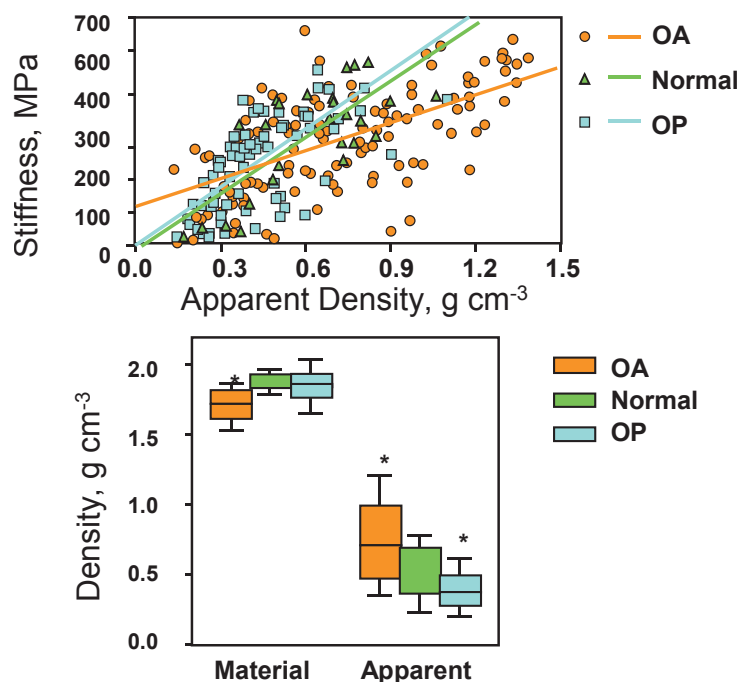


Fig. 11. The apparent density (bone mass/total volume) of bone in OA is significantly greater than normal (lower panel), but the material density (bone mass/bone volume) is significantly less. This confirms the density fractionation studies shown in Fig. 10. The upper panel shows the effect of this: as apparent density increases in OA (i.e., as the relative bone mass increases), there is a slower increase in the structural stiffness of the joint, because the material itself is less mineralized and therefore less stiff. (Reproduced from Reference ²⁴ with permission of the American Society for Bone and Mineral Research.)

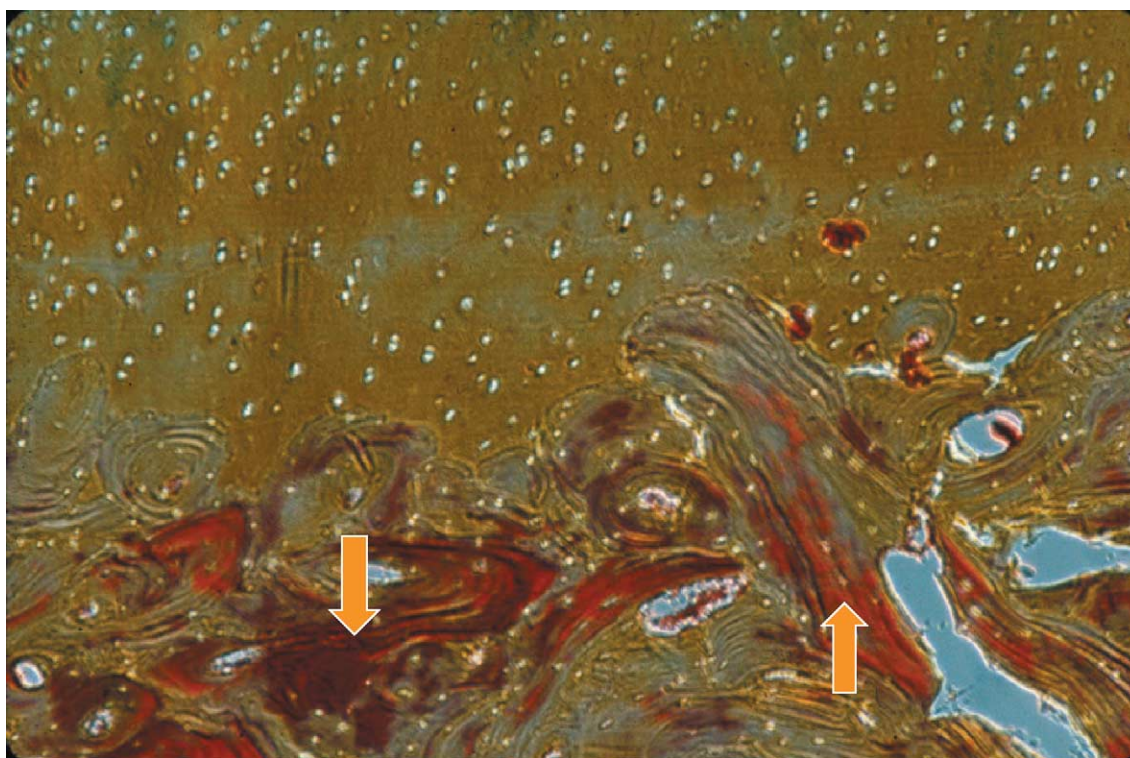


Fig. 12. Histological section of cartilage and subchondral bone from a rabbit proximal tibia following a period of impulsive loading. The increased rate of bone turnover, which would be associated with reduced tissue mineralization and stiffness, is clearly evident. The regions of bone that are stained darkly (red, arrows) are newer areas of bone that are not fully mineralized. (Pentachrome stain, Orig. mag.=25×).

[NSAIDs]) also eventually will reduce formation. Nevertheless, such treatments are likely to increase bone volume and density both by allowing refilling of the remodeling space without initiation of new sites of bone resorption, and by increasing the mean tissue age of the bone, allowing it to become more highly mineralized^{16,17}. Such 'anti-resorptive' treatments may also increase bone volume by inhibiting any resorption that occurs as the result of modeling, without inhibiting formation in the modeling mode. Finally, because modeling and remodeling are responsible for adapting the geometry of the joint to new conditions, anti-activation agents may prevent the normal alteration in joint shape that accompanies OA. As the alteration in joint shape is considered to be a positive adaptation to altered stresses associated with the breakdown of the joint, rather than a negative feature of the pathogenesis of OA, this could in the long run adversely affect the joint by increasing stresses in the overlying cartilage.

If increased bone stiffness is considered a predisposing factor for progression of OA, then treatments that increase stiffness are going to fail. However, if increased bone turnover is a predisposing factor to progression of OA, then treatments that reduce bone turnover may be beneficial. Currently, it is not clear which of these is the case as increases in both stiffness and turnover accompany progression of the disease. In actual fact, neither one may be causative. Therefore, before treatments can be designed to control progression of OA to full cartilage loss, much more must be learned about the pathogenesis of the disease itself.

Conclusion

There are several issues to consider in understanding the role of subchondral tissues in OA, and whether treatment of OA should begin with treatment of processes ongoing in the subchondral tissues. First, mineral content and thickness of calcified cartilage increase with age and probably in OA, and the possibility must be considered that the calcified cartilage has more of an effect on progression to cartilage loss than does subchondral bone. Second, there is both greater turnover and greater subchondral bone volume in OA, so that the tissue elastic modulus (material stiffness) is less but the structural stiffness of the bone is greater. The combined effects of these opposing processes on the joint are not at all clear. And finally, bone from the subchondral plate and subchondral trabecular bone must be distinguished morphologically, physiologically, and mechanically in discussions of the roles of subchondral bone in OA. These are different structures, and whatever changes occur in subchondral trabecular bone in OA are probably not causative to the progression to complete cartilage loss.

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